REMARKS

Status Summary

The request for continued examination (RCE) filed on April 13, 2005, was entered. Claims 56-60 and 62-74 are pending, which includes new claims 68-74, which were introduced with the RCE. Claims 56-60 and 62-67 remain rejected and claims 68-74 are newly rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of U.S. 6,042,826 to Caligiuri et al. (Caligiuri), and further in view of DeAngelis (1998) *J Neurooncology* 38:245-252 (DeAngelis). Claims 56-60 and 62-74 are also rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson).

A declaration by Ellen Garber, Ph.D. and pursuant to 37 C.F.R. § 1.132 is submitted herewith. Reconsideration in view of the declaration and following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 56-60 and 62-67 remain rejected and new claims 68-74 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. in view of U.S. 6,042,826 to Caligiuri et al., and further in view of DeAngelis (1998) J *Neurooncology* 38:245-252. The examiner's rejection with respect to claims 56-60 and 62-67 simply references the reasons set forth in the final official action and subsequent advisory action. With respect to the new claims, the examiner states that it would have been obvious to one skilled in the art to include radiolabeled or antibody-drug conjugates in the claimed therapeutic methods based on U.S. Patent No. 5,776,456 to Anderson et al. Specifically, the examiner points to text in the '456 patent that describes use of radiolabel or toxin to improve the efficacy of antibody treatment of B cell disorders (col. 4, lines 17+, of the '456 patent). Official action, pages 2-3.

Anderson describes methods for treatment of B cell lymphoma via administration of anti-CD20 antibodies. The examiner has previously noted that Anderson does not teach treatment of CNS lymphomas, as now claimed. The examiner concludes that it would have been *prima facie* obvious to modify the methods of Anderson to "include B-cell lymphomas

of the central nervous system because such lymphomas merely represent species of the broadly claimed genus of B-cell lymphomas." First official action (paper no. 7), pages 10-12.

The examiner relies on Caligiuri as teaching that primary CNS lymphomas involve the meninges, and on DeAngelis as teaching that lymphomas are a common cause of leptomeningeal metastases. Based thereon, the examiner concludes that one of ordinary skill in the art would reasonably expect that a subpopulation of patients with CNS lymphoma would also exhibit leptomeningeal lymphoma. Final official action (paper no. 20040722, pages 3-5. The examiner also relies on Caligiuri and DeAngelis as teaching combination of immunotherapy with chemotherapy, as in claims 4, 53, and 58. Final official action, (paper no. 20040722) pages 4-5, bridging paragraph.

In combining these references, the examiner has stated that "[w]hile the Caliguiri reference does not specifically teach administration of the claimed anti-CD20 antibodies, one of ordinary skill in the art who reads the Caliguiri reference would understand that the primary lymphomas of the CNS are treatable with antibodies – a lesson which is particularly relevant to the teachings of the Anderson patent which also concludes that lymphomas (in general) can be treated with antibodies." Advisory action, page 3, lines 16-20 (emphasis in original).

The foregoing rejection and analysis of the cited references is respectfully traversed as follows.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. *See also In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). *See also, Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). That is, at the time of the invention, one skilled in the art must believe that the claimed methods could be practiced with a reasonable expectation of success. Here applicant contends that, after a review of the cited references, one skilled in the art would not reasonably believe that the presently claimed methods could be practiced with an expectation of achieving therapeutic efficacy. Thus, applicant submits that the examiner has failed to meet the mandated burden.

More particularly, applicant strongly contends that, at the time of filing the instant application, a skilled artisan would not believe that there was a reasonable chance of success in practicing the claimed invention due to the inherent unpredictability in treatments for CNS lymphomas. As previously indicated, Anderson does not provide specific guidance with respect to CNS malignancies. The DeAngelis and Caligiuri references, which describe intrathecal administration of chemotherapeutic chemicals and antibodies, respectively, do not provide any suggestion whatsoever that the presently claimed anti-CD20 therapies could be reasonably employed in the treatment of CNS malignancies, and therefore, cannot cure the inherent deficiency of Anderson.

In further support of this position, applicant submits herewith a declaration pursuant to 37 C.F.R. § 1.132. Based upon her education and experience in developing antibody therapies, the affiant, Dr. Ellen Garber, qualifies as one of skill in the art at the time of filing of the instant application. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 1-4. Accordingly, her viewpoint regarding the expectation of success in performing the claimed invention is relevant to a determination of non-obviousness of the invention.

As a skilled artisan in the field of study of the instant application, Dr. Garber contests the examiner's conclusion that the combined teaching of the Anderson, Caligiuri, and DeAngelis references renders obvious the presently claimed invention. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 5-10. In particular, Dr. Garber presents evidence that the cited documents are not reasonably predictive of the success of anti-CD20 therapy for the treatment of CNS lymphomas, notwithstanding the success of systemic anti-CD20 therapy. As described further below, Dr. Garber disagrees with the examiner's analysis in that it focuses on the mechanics of intrathecal antibody administration without considering the biological basis of particular treatments.

DeAngelis is a review article that states that intrathecal chemotherapy is a mainstay treatment for leptomeningeal metastasis and that this treatment is usually well-tolerated. *See* page 249, column 1. Contrary to the position of the examiner, one skilled in the art would not conclude that the ongoing use of chemotherapy drugs by intrathecal administration, as summarized by DeAngelis, has predictive value regarding the therapeutic efficacy or safety of other drugs (particularly biologics). *See* Declaration by Ellen Garber, Ph.D., ¶¶ 11-15. DeAngelis identifies three chemotherapeutic drugs that are commonly used for treatment of leptomeningeal metastasis: methotrexate, cytarabine, and thiopeta. *See* page 249, column 2.

The chemotherapeutic agents described by DeAngelis are small inorganic chemicals, which are completely different molecular entities, and have completely different physiochemical properties, than large, biologically complex antibodies. Applicant submits that the completely different physiochemical properties of the claimed biologics *vis-à-vis* the agents of DeAngelis preclude any meaningful comparison with respect to administration, pharmacodynamics, dosing, *etc.* Moreover, the mode of action of the agents disclosed in DeAngelis is completely different from the presently claimed antibodies. In this regard, the anti-cancer activity of many classical chemotherapeutic drugs generally lies in their ability to disrupt basic cellular activities of actively dividing cells. For example, methotrexate and cytarabine are antimetabolites that interfere with nucleic acid synthesis by inhibiting folate metabolism. Conversely, the therapeutic efficacy of the claimed targeting antibodies relies upon the cytotoxicity of associated molecules and/or cytotoxicity mediated by effector functions found in the antibody constant regions.

Notwithstanding the above-noted structural differences and distinct modes of action of chemotherapeutic drugs as compared to therapeutic antibodies, Dr. Garber also notes that direct brain administration of any therapeutic agent remains highly unpredictable due to the unique brain environment and the risks of neurotoxicity. *See* Declaration by Ellen Garber, Ph.D., ¶ 16. In response to applicant's prior arguments regarding the known risks of toxicity following direct brain administration, the examiner states that the requirements for demonstrating therapeutic utility are distinct from FDA requirements for drug safety. Official action, page 4. Applicant acknowledges as correct the examiner's statement that the criteria for establishing patentable *utility* of a substance are distinct from the requirements for FDA approval, noting however that this distinction does not bear on the non-obviousness of a new therapeutic method employing that substance.

Applicant also strongly contests the examiner's conclusion that treatment of CNS lymphomas by intrathecal administration of anti-Fas antibodies, as described in the Caliguiri patent, is relevant to the potential therapeutic efficacy of anti-CD20 antibodies for treating CNS lymphomas. Applicant acknowledges that Caligiuri describes intrathecal antibody administration, however any efficacy of anti-Fas antibodies is not at all relevant to the therapeutic efficacy of anti-CD20 antibodies. As detailed below, a skilled artisan would not conclude that the efficacy of intrathecally administered anti-CD20 antibodies could be reasonably predicted based upon the use of anti-Fas antibodies given that anti-Fas antibodies

and anti-CD20 antibodies (a) recognize distinct antigens having unique expression profiles, and (b) confer therapeutic effects by entirely different modes of action. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 17-36.

The Caliguiri patent describes treatment of primary central nervous system lymphoma (PCNSL) using a Fas-cross-linking composition to elicit Fas-mediated cytotoxicity. The Caliguiri patent states that the Fas-cross-linking composition can be an anti-Fas antibody having agonist activity or soluble Fas ligand. Fas, also called APO-1 or CD95, is a transmembrane receptor that is a member of the tumor necrosis factor (TNF) receptor family, which trigger apoptosis by activating a cascade of specific proteases called caspases. The activated caspases cleave cellular components, a process that leads to morphological cellular and nuclear changes as well as to degradation of chromosomal DNA.

Initially, applicant submits that any therapeutic success obtained in targeting Fas antigen is not predictive of potential therapeutic success in targeting the CD20 antigen, even if both antigens are expressed on malignant cells of the same lineage. The inability to extrapolate the suitability of one antigen target for another stems from differences in antigen expression profiles, including antigen localization (*i.e.*, intracellular or membranous, or a combination thereof), antigen density, antigen expression levels, antigen expression on malignant cells as compared to normal cells, antigen expression on subpopulations of malignant cells, antigen expression at particular times of the cell cycle, antigen half-life, antigen glycosylation and other post translational modifications that affect antigen accessibility, stability / strength of binding to an antibody, and antigen internalization upon antibody binding.

In addition to targeting of different antigens, anti-Fas and anti-CD20 antibodies operate via different modes of action. More specifically, in contrast to the agonistic anti-Fas antibodies described in Caliguiri, the therapeutic efficacy of anti-CD20 antibodies primarily relies on induction of antibody-dependent cell-mediated cytotoxicity (ADCC) and cell dependent cytotoxicity (CDC), which each involve immune system effector cells, *i.e.*, NK cells and macrophages, to effect lysis of antibody-targeted cells. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 22-30. Induction of apoptosis has been described as a third therapeutic mechanism of anti-CD20 antibodies, which also requires the presence of secondary IgG antibodies or FcR-expressing cells. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 33-34. The therapeutic efficacy of anti-CD20 antibodies, which requires recruitment of immune cells, is

different from that of anti-Fas antibodies, which relies on direct induction of apoptotic changes within tumor cells (*i.e.*, without the action of lymphoid and myeloid effector cells). Further, although the CNS exhibits some innate immune responses, including NK and macrophage activity, immune inhibitory and anti-inflammatory mechanisms physiologically outbalance and counteract immune activity and thereby limit immune-mediated tissue damage in the brain. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 31-32. The dependence on immune system effector cells, whose activity is limited in the CNS, is one reason why the therapeutic efficacy of anti-CD20 antibodies in the treatment of CNS lymphomas was unexpected. Therefore, at the time at which the instant application was filed, the use of anti-CD20 antibodies for the treatment of CNS lymphomas was unpredictable notwithstanding the success of intravenously administered systemic rituximab for non-CNS lymphomas or therapies employing apoptotic inducing antibodies such as anti-Fas antibodies. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 34-36.

Accordingly, DeAngelis fails to cure the deficiency of Anderson with respect to specific guidance for treatment of CNS malignancies based upon clear physochemical differences and disparate modes of action between the small inorganic chemotherapeutic agents described by DeAngelis and the large biological anti-CD20 antibodies of the present invention. Caliguiri also fails to cure the deficiency of Anderson based upon targeting of different antigens (Fas and CD20, respectively) and different modes of action of the anti-Fas antibodies of Caliguiri as compared to the anti-CD20 antibodies of the present invention.

Based on the foregoing, and the declaration submitted herewith, one skilled in the art would not be motivated to replace the anti-Fas antibody in the methods of DeAngelis or Caliguiri with an anti-CD20 antibody of Anderson to arrive at the presently claimed invention. In the absence of a motivation to practice the claimed invention based on a reasonable chance of success, the claims are not *prima facie* obvious. Accordingly, applicant respectfully requests that the rejection of claims 56-60 and 62-74 under 35 U.S.C. § 103(a) based on Anderson, Caligiuri, and DeAngelis be withdrawn.

Rejection of Claims Based on Non-Statutory Obviousness-Type Double Patenting

Claims 56-60 and 62-67 remain rejected and new claims 68-74 are rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456. The examiner's basis for rejection is the same as that set forth

above with respect to 35 U.S.C. § 103(a). Official action, page 4. This rejection is respectfully traversed.

Based on the arguments set forth above in response to the rejection of claims under 35 U.S.C. § 103(a), which are incorporated herein, applicant believes that the methods of the present disclosure are non-obvious in view of Anderson. As such, applicant also requests that the obviousness-type double patenting rejection be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,
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